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Optimizing Selection on Major Genes

Abstract

Molecular genetics technology is leading to the discovery of individual genes with large effects for traits of interest in swine. Although the use of such major genes can enhance rates of genetic improvement in the short term, their injudicious use can lead to less response to selection in the longer term. This article describes the development of a method to optimize the use of a major gene in selection. Results show that optimal strategies for selection on the major gene can lead to increased response to selection, in particular for major genes that show dominance. The results imply that major genes can substantially enhance rates of genetic improvement in both the short and long term, provided selection on the major gene is integrated properly within existing selection strategies. Thus, the use of major genes in selection, requires careful formulation of the objectives and strategies for selection. The methods developed in this research provide a framework to formulate such strategies. Further extension of methods to deal with the complexities of practical breeding programs is, however, required.

Keywords

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Optimizing Selection on Major Genes

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Summary and Implications

Molecular genetics technology is leading to the discovery of individual genes with large effects for traits of interest in swine. Although the use of such major genes can enhance rates of genetic improvement in the short term, their injudicious use can lead to less response to selection in the longer term. This article describes the development of a method to optimize the use of a major gene in selection. Results show that optimal strategies for selection on the major gene can lead to increased response to selection, in particular for major genes that show dominance.

The results imply that major genes can substantially enhance rates of genetic improvement in both the short and long term, provided selection on the major gene is integrated properly within existing selection strategies. Thus, the use of major genes in selection, requires careful formulation of the objectives and strategies for selection. The methods developed in this research provide a framework to formulate such strategies. Further extension of methods to deal with the complexities of practical breeding programs is, however, required.

Introduction

To date, most genetic improvement in swine has been achieved through selection on phenotypic performance or on estimated breeding values (EBV) that are based on phenotype. Current advances in molecular genetics are, however, leading to the discovery of individual genes with substantial effects on traits of economic importance. Examples of these so-called major genes are the halothane gene and the Estrogen Receptor Gene (3). Other examples, including the RN gene for meat quality, are just around the corner.

The use of major genes in breeding programs has the potential to substantially enhance rates of genetic improvement by being able to directly select the genes that affect performance. Selection should, however, not be based exclusively on the major gene. Such a strategy would ignore all the other genes that affect performance. These unknown or unidentified genes will be referred to as polygenes in what follows. It is well established that selection on EBV from phenotype is an effective means for improving these polygenes and the power of such EBV would be ignored if selection were exclusively on the major gene. To make maximum genetic progress, selection must be on a combination of the animal's (known) genetic value for the major gene plus the animal's EBV for polygenes.

Theoretically, simply adding the animal's genetic value or breeding value for the major gene to the animal's EBV for polygenes provides the most accurate estimate of the animal's total breeding value. Most strategies for selection on a major gene are currently based on such a selection criterion. Research by Gibson (2), however, showed that, although selection on such a combined criterion increases response to selection in the short term, it does not maximize rates of genetic improvement in the longer term. In fact, using computer simulation, Gibson (2) found that selection on phenotypic information alone resulted in greater genetic improvement in the longer term than combined selection based on the major gene and phenotype. His results are illustrated in Figure 1 for selection of 20% of males and females for a trait with heritability 25%, a phenotypic standard deviation of 1, and for an additive major gene with an initial frequency of 5% and a difference of one phenotypic standard deviation between homozygotes.

As shown in Figure 1, phenotypic and combined selection both resulted in an increase in the frequency of the major gene. Although combined selection resulted in a more rapid increase in frequency of the major gene, this was at the cost of genetic response in the polygenes. Although combined selection recovered some of this lost polygenic response after the major gene was fixed, it was never able to recover all lost response.

The conclusion to be drawn from this and related studies is that, although knowledge of a major gene should enhance rates of genetic improvement, we currently do not know how to use these major genes to the best of our advantage. The objective of this research was therefore to develop selection strategies that optimize the use of a major gene in a genetic improvement program.

Materials and Methods

In this study, a simplified genetic model was used to develop strategies that optimize selection on a major gene. In this model, selection was for a single trait that was determined by an identified major gene and a large number of polygenes, along with environment. Polygenic variance was assumed constant.

The following general selection criterion was considered: $I = b \times (\text{Major Gene BV}) + (\text{Polygenic EBV})$. This criterion combines the breeding value (BV) for the major gene, which was assumed known, with an estimate of the BV for polygenes, which was based on phenotype. The relative emphasis on the major gene versus polygenes is determined by the weighting factor b . In current strategies for selection on a major gene, as defined by Gibson (1994) and others, b is equal to 1. These strategies will be referred to as standard (major gene) selection. Our objective was to find the weighting factors b that resulted in maximum response after a given number of generations of selection.

Resulting strategies will be referred to as optimal (major gene) selection.

An optimization method called optimal control theory was used to find the optimal weights. Optimal control theory is a method that is used extensively in engineering and economics and is particularly suited to optimize selection over more than one generation. Optimal strategies were compared with current selection strategies.

Results and Discussion

Using optimal control theory, an iterative computing algorithm was derived with which index weights that maximize response after a given number of generations can be obtained. Details can be found in Dekkers and van Arendonk (1).

Results for selection on an additive major gene to maximize selection after 5 or 10 generations are summarized in Figure 2. Results are for selection of 20% of males and females for a trait with heritability 25%, a phenotypic standard deviation of 1, and for an additive major gene with an initial frequency of 5% for the favorable allele, and a difference of one phenotypic standard deviation between homozygotes. Results show that optimal selection achieved greater response at the end of the planning horizon (i.e. after 5 or 10 generations) than standard major gene selection. Extra responses of up to 3% were obtained. Optimal strategies also resulted in greater improvement than phenotypic selection.

Figure 2c shows the index weights that maximized response after 10 generations. Optimal weights changed from generation to generation and in general were lower than 1, which is the weight used in standard major gene selection. Weights also differed depending on whether the individual had the unfavorable genotype for the major gene (bb) or the favorable genotype (BB): weights were higher for the bb genotype. This suggests that the optimal strategy selected more heavily against bb than in favor of BB, relative to the heterozygote (Bb). The optimal weights resulted in a more gradual increase in frequency of the major gene (Figure 2a) and a nearly constant rate of improvement in polygenes (Figure 2b), in contrast to standard major gene selection.

Figure 2 was for a trait with heritability of 25%. Figure 3 shows the extra responses that can be obtained from optimal selection on a major gene relative standard major gene selection for traits with different heritabilities. For a trait with heritability equal to 5%, up to 6% greater response was obtained from optimal selection, even after 3 generations.

Figures 2 and 3 focused on a major gene with additive effects and no dominance. This means that the heterozygote (Bb) has an effect that is intermediate to that of the two homozygotes (bb and BB). For such genes, modest increases in response to selection were obtained from optimization. Figure 4 shows that for genes with dominance, optimal selection resulted in substantially greater extra

responses. For a major gene with overdominance (i.e., the heterozygote has a greater value than the best homozygote), extra responses of over 6% were obtained after 5 generations.

For genes with additive effects, standard major gene selection maximizes response to selection after one generation. This is, however, not true when the gene is dominant, in which case optimization can result in greater responses even after one generation. Results summarized in Figure 5 indicate that increases in response to selection of up to 9% over a single generation can be obtained when the major gene shows (over-) dominance.

Jointly, these results show that selection on a major gene can be optimized. If optimal strategies are used, substantial extra rates of genetic improvement can be obtained in both the short and the longer term. Development of optimal strategies does require the breeder to carefully establish a planning horizon and selection objective. In the current study, the selection objective was defined as maximizing cumulative response after a number of generations. Work is currently ongoing to develop selection strategies that maximize a combination of short and longer-term responses, with more emphasis on short-term gains. In addition, work is ongoing to extend the method to include the complexities of practical breeding programs, and simultaneous selection on several major genes, and on linked genetic markers. The method developed in this research provides the framework to derive selection strategies that optimize the use of molecular genetic information under such circumstances.

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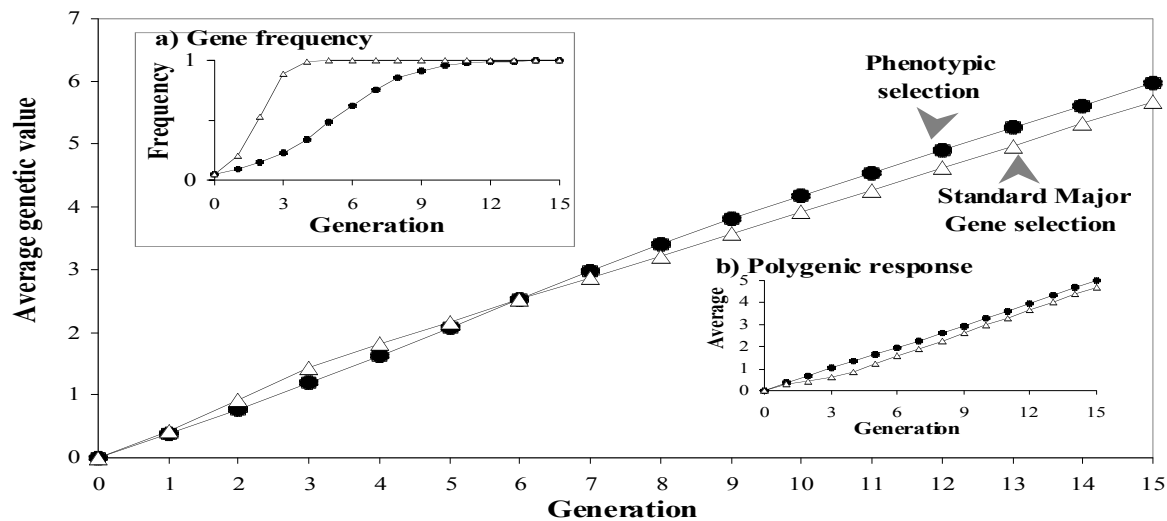


Figure 1. Illustration of the effect of standard major gene selection on an additive major gene (Δ) versus selection on phenotype (\bullet).

Main graph: Cumulative response in the total average genetic value in the population.

a) Effect of selection on the frequency of the favorable allele for the identified gene.

b) Cumulative response in average polygenic effects.

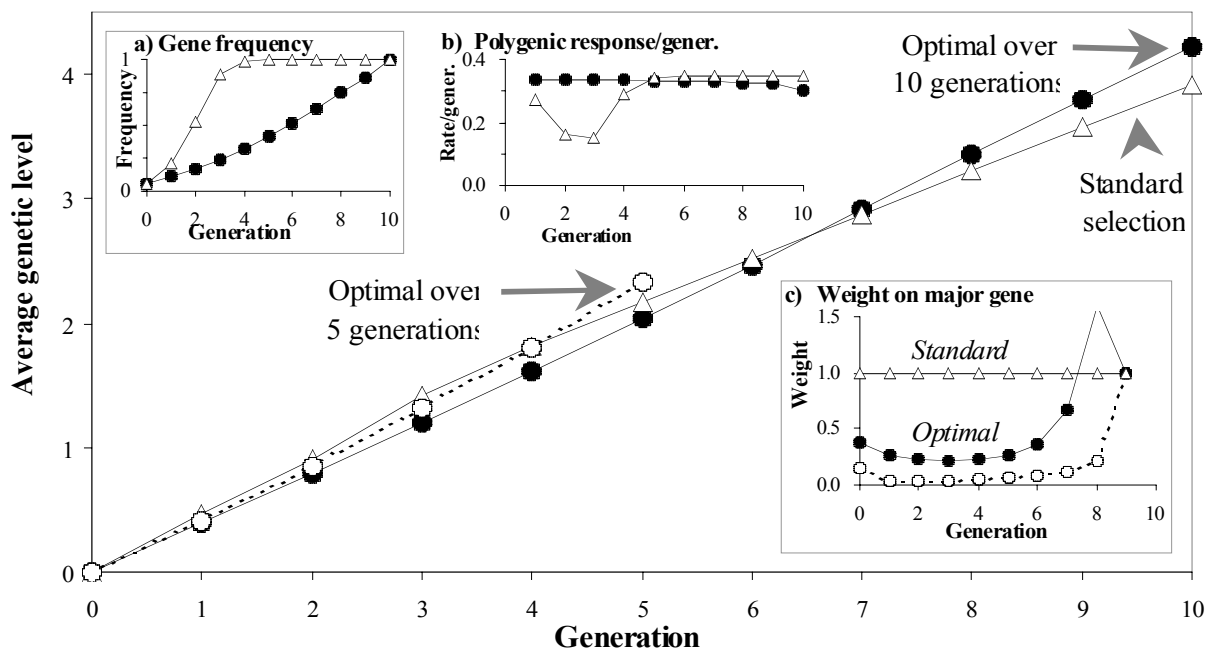


Figure 2. Comparison of optimal (\bullet and O) to standard (Δ) strategies for selection on an additive major gene.

Main graph: Effect of selection on cumulative response in the average genetic level. For optimal selection, results are shown for selection strategies that maximize response after 5 (O) or 10 (\bullet) generations

a) Effect on frequency of the favorable allele for the major gene.

b) Effect on the rate of increase in the average polygenic effect per generation.

c) Weights on the major gene for standard and optimal selection over 10 generations. For optimal selection, weights depend on whether the individual is homozygous favorable (O) or unfavorable (\bullet).

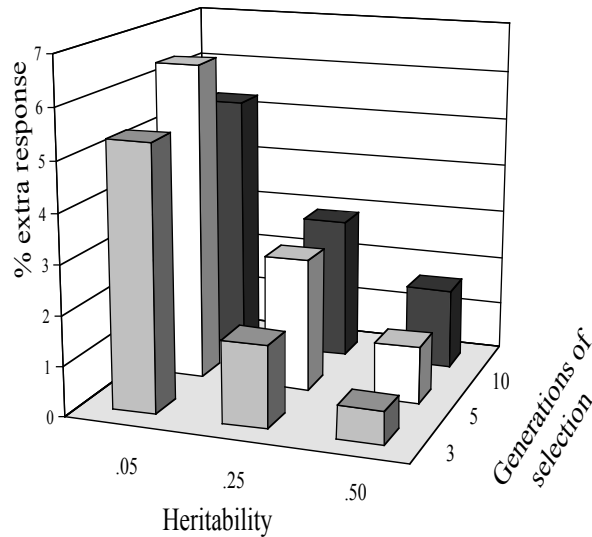


Figure 3. Extra response from optimal selection on an additive major gene as a percentage of response for standard major gene selection for different heritabilities and planning horizons (maximizing response over 3, 5, or 10 generations). Results are for a gene with two additive alleles with a difference of 1 genetic standard deviation between homozygotes. Initial gene frequency is 0.25 and 20% of males and females are selected.

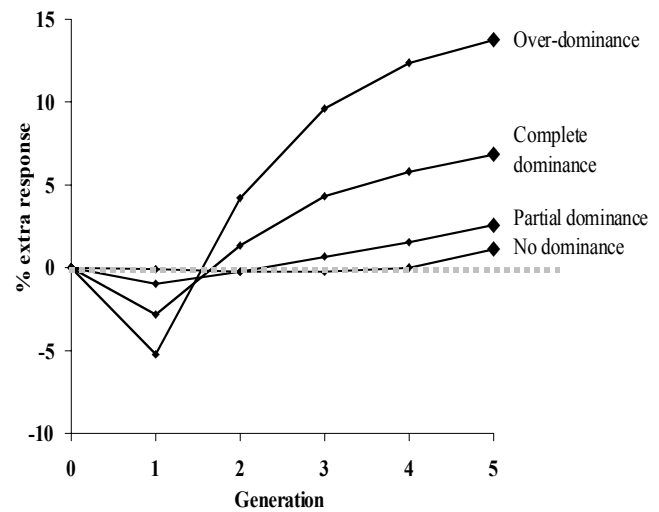


Figure 4. Effect of dominance at the major gene on extra cumulative response from optimal selection to maximize response after 5 generations as a percentage of response for standard major gene selection. Results are for a gene with two additive alleles with a difference of 1 genetic standard deviation between homozygotes. Initial gene frequency is 0.25 and 20% of males and females are selected.

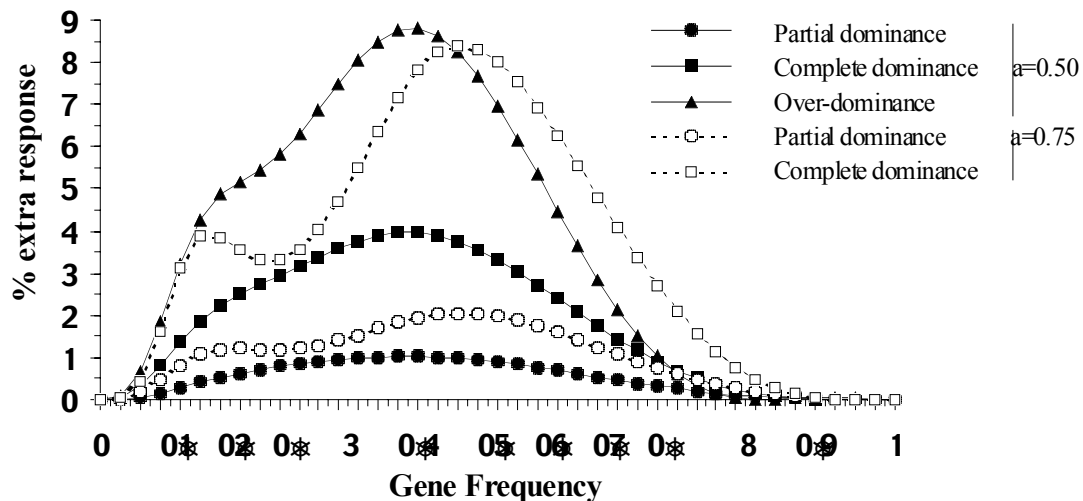


Figure 5. Extra response from optimal selection on a major gene over a single generation, as a percentage of response to standard major gene selection for a gene with different degrees of dominance. Results are for a major gene with additive effects (a =difference between homozygotes) of 0.5 or 0.75 phenotypic standard deviations. Heritability is 0.25 and 20% of males and females are selected.